To: BLA STN 103628/5021 (Biogen Avonex, Interferon beta-1a for MS)
From: Gary Kikuchi/Elizabeth Shores
Through: Amy Rosenberg, Director, DTP
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Immunogenicity Review for Avonex HuSA-Free Liquid Presentation Supplement

Administrative

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Action due date: May 28, 2002

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Recommendation: All immunogenicity issues have been adequately addressed and approval is recommended.

I. Summary/Background

Rationale: This sBLA submission (103628/5021) (HuSA-free supplement) is for a HuSA-free liquid presentation of Avonex, (Interferon beta-1a for multiple sclerosis). Because of this formulation change, the sponsor was asked to address the potential immunogenicity of the product.

Background: The immunogenicity assay used in this HuSA-free supplement is the one fully described in another supplement, STN 103628/5008 (NAB supplement), which is was completely reviewed by Gary Kikuchi and approved on November 12, 20002 A two part screening method is used; an ELISA screening assay and a neutralization assay. Complete assay methods and validation are described in a review dated August 21, 2002 of the NAB supplement.

The immunogenicity information contained in the HuSA-free supplement is from clinical trial C98-844. This was a multi-center, single-arm, open label study of 153 MS patients (intent-to-treat basis) treated with serum-free Avonex at 30 mcg weekly IM. Presence of antibodies was determined using the assays described briefly below. The sponsor stated that the incidence of immunogenicity observed in this clinical trial

with the liquid formulation was similar to the incidence found in previous clinical trials found with the lyophilized formulation of Avonex (BG9418).

II. Summary of Immunogenicity assays

The assays used to assess product immunogenicity are described in reviews dated January 24, 2002 and August 21, 2002 of the NAB supplement. The Biogen assay uses two steps, a screening ELISA and a neutralization assay. These assays are briefly summarized as follows:

1. Biogen Screening ELISA. The screening ELISA is a [redacted]

2. Biogen Neutralization Assay. Neutralizing antibody is detected by its ability to neutralize the protective effect of interferon beta in a cytopathic effect (CPE) assay. In this assay, [redacted]

Complete methods and validation for these assays have been submitted to sBLA STN 103628/5008 (NAB supplement) and are reviewed in a document dated August 21, 2002.

VI. Clinical Immunogenicity Information

Early Analysis:
153 MS patients were enrolled in clinical study C98-844 and were to receive Avonex pre-filled syringes (30 mcg IM weekly) for up to three years. Interim data is reported in the sBLA, including 127 patients that had NAB data up to 12 months. 12 months is stated by the sponsor to be adequate to evaluate the immunogenicity of Avonex.

In the clinical summary, the sponsor states that 5/150, (3.3%) of the patients had neutralizing titers >=5 at some time during the course of the study.

Problems/Caveats/Comments:

Close examination (in collaboration with the statistical reviewer) of the clinical database, [redacted], provided by the sponsor, yields an incidence rate that differs slightly from that stated by the sponsor. The following table shows all neutralizing titers greater than zero for the clinical trial:

Neutralizing titers greater than zero in C98-844 by month						
	Month					
	9	12	15	18	21	24
102003	0	0	0	30	270	ND
106003	ND	0	0	4	0	ND
106007	ND	5	30	13	13	ND
106009	0	0	30	0	0	ND
204001	0	23	270	810	810	ND
301014	2	0	0	0	0	ND
307006	0	0	4	0	ND	ND
307007	0	0	0	30	ND	ND

Five patients, 102003, 106007, 106009, 204001, and 307007, had positive titers greater than or equal to 5 during the trial.

In a follow-up teleconference of April 4, 2003, Dr. Walton (FDA) asked Biogen if immunogenicity rates were based on a titer great than or equal to 5 (consistent with what was done previously). Biogen responded yes. Biogen also commented that the denominator is 129 and is the number of patients remaining in the study at 12 months; the number of patients most at risk. Biogen stated that there were 5 patients who tested positive out of 129. Biogen stated that there were 5 patients who tested positive up to 12 months and 3 additional patients who tested positive later in the trial at 18 months. Dr. Walton informed Biogen that all of the patients who tested positive should be included. Therefore, the numerator is 8 and the denominator is 129 (8/129=6.2%).

The incidence of serum NAB reported in the labeling for the 5008 and 5001 supplement, testing the HuSA-containing material reported 13/261 or 5% which is very similar to that of this current formulation without Hu-SA.

VI. Complete Review comments (sent November, 2002)

5. The Biogen assay used to detect antibodies to Avonex used in clinical trial C98-844, entitled "A Multicenter, Open-Label, Antigenicity and Safety Study of a Human Serum Albumin-Free Pre-Formulated Solution of Avonex, Interferon beta-1a Administered Intramuscularly to Patients with Relapsing Multiple Sclerosis," consists of a screening ELISA, using a [redacted], and a neutralizing antibody assay. The [redacted] may have the potential to [redacted] This concern is supported by data you have published in which you demonstrate that the [redacted], and that at least one

clinical sample was not positive in the ——— ELISA, but was positive in an ELISA with a different design.

This issue was completely addressed in the context of the 5008 (NAB supplement). See Immunogenicity Review memo for 103628/5008 supplement of November 6 2002.

6. *In clinical trial C98-844, the submission states that 5 out of 150 patients were positive for antibodies to Avonex, based on 12-month interim data. However, our analyses of the database revealed the following:*

   a. *4 out of 5 of these patients had titers that were positive only at 15 months or after, and that only 128 patients in the trial had antibody data collected at 15 months. Therefore, we calculate the incidence rate of patients with antibody titers ≥ 5 as 5 out of 128 or 3.9%.*

   b. *the incidence rate of antibodies in patients treated with IFN-β 1a should be expressed based on analysis of samples collected at a minimum of 18 months of treatment. Please comment.*

The sponsor has submitted data and reanalyzed immunogenicity incidence rates using time points and patient numbers. The final agreed upon labeling reflects those changes. The response is adequate.

7. *Please provide a timeline for submission of the final immunogenicity results from clinical trial C98-844.*

The sponsor's response of November 22, 2002 contained the final clinical study report for C98-844, which is based on the analyses of the full data set, covering 24 months of treatment and follow-up. The response is adequate.

V. Labeling

The original PI submitted with the supplement contained information specific to the HuSA-free formulation. In a teleconference of April 4, 2003, FDA informed Biogen that the information on the HSA-free formulation should be incorporated into the current package insert (for the Hu-SA-containing product) rather than in a separate package insert. Consequently, the immunogenicity data obtained from studies obtained with both forms of product were merged, leading to an overall NAB immunogenicity rate of 21/390 or 5.3 %

DTP Suggested Final Labeling

As with all therapeutic proteins, there is a potential for immunogenicity. In recent studies assessing immunogenicity in multiple sclerosis patients administered AVONEX for at least 1 year, 5% (21 of 390 patients) showed the presence of

neutralizing antibodies at one or more times. The clinical significance of neutralizing antibodies to AVONEX is unknown.

The data reflect the percentage of patients whose test results were considered positive for antibodies to AVONEX® using a two-tiered assay (ELISA binding assay followed by a antiviral cytopathic effect assay), and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of neutralizing antibody activity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to AVONEX® with the incidence of antibodies to other products may be misleading